Extended-pulsed fidaxomicin versus vancomycin for Clostridium difficile infection in patients 60 years and older (EXTEND) : a randomised, controlled, open-label, phase 3b/4 trial

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Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial

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Summary

Background ***Clostridium difficile*** **infection causes severe complications and frequently recurs. An extended-pulsed fidaxomicin regimen might facilitate sustained clinical cure by prolonging *C difficile* suppression and supporting gut microbiota recovery. We aimed to compare clinical outcomes of extended-pulsed fidaxomicin with standard vancomycin.**

Methods In this randomised, controlled, open-label, superiority study, we recruited hospitalised adults aged 60 years and older with confirmed *C difficile* infection at 86 European hospitals. Patients were randomly assigned (1:1) using an interactive web response system to receive extended-pulsed fidaxomicin (200 mg oral tablets, twice daily on days 1–5, then once daily on alternate days on days 7–25) or vancomycin (125 mg oral capsules, four times daily on days 1–10), stratified by baseline *C difficile* infection severity, cancer presence, age (≥75 years *vs* <75 years), and number of previous *C difficile* infection occurrences. The primary endpoint was sustained clinical cure 30 days after end of treatment (day 55 for extended-pulsed fidaxomicin and day 40 for vancomycin), assessed in all randomised patients who met the inclusion criteria and received at least one dose of study medication (modified full analysis set). Adverse events were assessed in all patients who received at least one dose of study drug. The study is registered with ClinicalTrials.gov, number NCT02254967.

Findings Between Nov 6, 2014, and May 5, 2016, 364 patients were enrolled and randomly assigned to receive extended-pulsed fidaxomicin or vancomycin. 362 patients received at least one dose of study medication (181 in each group). 124 (70%) of 177 patients in the modified full analysis set receiving extended-pulsed fidaxomicin achieved sustained clinical cure 30 days after end of treatment, compared with 106 (59%) of 179 patients receiving vancomycin (difference 11% [95% CI 1·0–20·7], p=0·030; odds ratio 1·62 [95% CI 1·04–2·54]). Incidence of treatment-emergent adverse events did not differ between extended-pulsed fidaxomicin (121 [67%] of 181) and vancomycin (128 [71%] of 181) treatment arms. One death in the vancomycin arm was considered by the investigator to be related to study drug.

Interpretation Extended-pulsed fidaxomicin was superior to standard-dose vancomycin for sustained cure of *C difficile* infection, and, to our knowledge, extended-pulsed fidaxomicin recurrence rates in this study are the lowest observed in a randomised clinical trial of antibiotic treatment for *C difficile* infection.

Funding Astellas Pharma, Inc.

Introduction

Clostridium difficile is the leading cause of infectious health-care-associated diarrhoea in developed countries.[1] *C difficile* infection is particularly serious in older individuals, in whom it is associated with severe infection and complications, including recurrence and death.[2–4]

Prevention of recurrence of *C difficile* infection has been identified as a key unmet need.[5] Recurrence is estimated to occur in up to 25% of patients treated with metronidazole or vancomycin,[5,6] is associated with a substantial health-care burden,[6] and is a particular problem in high-risk individuals.[7] Previous administration of antimicrobials typically results in disruption of the colonic microbiota, preceding *C difficile* colonisation.[8,9] Recurrence is thought to be a consequence of delayed recovery of this previously disrupted microbiota during *C difficile* infection therapy.[8] Although oral vancomycin is the standard of care for severe *C difficile* infection,[3] this drug has a substantial deleterious effect on the intestinal bacterial microbiota.[10,11]

The narrow-spectrum macrocyclic antibiotic fidaxomicin showed efficacy and tolerability for treatment of *C difficile* infection when administered as a standard regimen (200 mg orally twice daily for 10 days), and is non-inferior to standard vancomycin (125 mg orally four times daily for 10 days) in achieving initial clinical cure.[12,13] Fidaxomicin is better able to preserve the gut microbiota than is vancomycin,[10] which might explain

Research in context

Evidence before this study

Metronidazole and vancomycin have been the mainstays of *Clostridium difficile* infection treatment for several decades, with vancomycin efficacy superior to that of metronidazole. We searched PubMed for articles published in any language up to March 6, 2017, using the terms "*Clostridium difficile* infection" and "recurrence". We identified several studies and reviews that reported recurrence rates of up to 25%. We noted advanced age as a risk factor for *C difficile* infection recurrence and adverse outcomes following treatment. In fidaxomicin phase 3 registration studies, more than half of patients were at least 60 years of age. These studies were the first to show that fidaxomicin was non-inferior to vancomycin for clinical cure, but also associated with a reduction in *C difficile* infection recurrence compared with vancomycin. Adjunctive therapy with the monoclonal antibody bezlotoxumab plus standard of care showed a reduction in *C difficile* infection recurrence compared with placebo at 12 weeks post-infusion. In-vitro gut model evidence supports the potential benefits of an extended-pulsed fidaxomicin treatment regimen with respect to rapid clearance of *C difficile* while simultaneously supporting recovery of microbiota that are important for subsequent colonisation resistance. Evidence for alternative fidaxomicin dosing strategies, including chaser and pulsed regimens for recurrent *C difficile* infection, is limited to small case series, as is evidence for pulsed regimens of vancomycin.

Added value of this study

This phase 3b/4 study shows superiority of extended-pulsed fidaxomicin over standard vancomycin in achieving sustained clinical cure of *C difficile* infection in an older patient population. Addition of a pulsed fidaxomicin dosing period did not adversely affect rates of initial clinical cure and resulted in reduced *C difficile* infection recurrence rates compared with vancomycin. The recurrence rate with extended-pulsed fidaxomicin treatment, monitored over 90 days, is the lowest reported to our knowledge in a randomised controlled trial of *C difficile* infection antibiotic treatment. Furthermore, disease-free survival was higher in extended-pulsed fidaxomicin patients compared with patients receiving vancomycin. Addition of novel exploratory microbiology endpoints also allows interpretation of microbiome diversity, for the first time to our knowledge, in a *C difficile* infection-targeting antibiotic randomised controlled trial. The shift in bacterial diversity up to day 55 was greater in extended-pulsed fidaxomicin patients compared with vancomycin patients, which supports the hypothesis that extended-pulsed fidaxomicin facilitates recovery of the microbiota during treatment. Sustained efficacy with the extended-pulsed fidaxomicin regimen was achieved with no increase in treatment costs and no detriment to safety compared with standard-regimen vancomycin and fidaxomicin.

Implications of all the available evidence

Prevention of recurrence of *C difficile* infection is recognised as a key unmet clinical need, particularly in high-risk populations, such as older patients. The EXTEND study addresses sustained cure as a primary measure of treatment success in a high-risk patient population, with recurrence monitored up to day 90. To our knowledge, this study provides the first clinical evidence for extended-pulsed fidaxomicin as an efficacious and well-tolerated treatment option for *C difficile* infection. Available in-vitro and clinical evidence suggests that the sparing effect of fidaxomicin on the gut microbiota might contribute to observed treatment outcomes.

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See Online for appendix

the well-documented reduced *C difficile* infection recurrence (about 15%) and improved sustained clinical cure (about 75%) with fidaxomicin compared with vancomycin (about 27% for *C difficile* infection recurrence and 64% for sustained clinical cure).[12,13]

Evidence from a validated in-vitro human gut model suggests that an extended-pulsed fidaxomicin regimen, which extends 20 fidaxomicin doses over a longer time period after initial daily dosing, might allow persistence of fidaxomicin at above inhibitory concentrations, thus prolonging suppression of *C difficile*, and simultaneously facilitating microbiota recovery.[14] Consequently, extended-pulsed fidaxomicin is hypothesised to show equivalent efficacy to vancomycin in resolving *C difficile* infection. This drug regimen might also have the potential to reduce *C difficile* infection recurrence beyond that documented for standard fidaxomicin and increase sustained clinical cure.

We aimed to assess clinical outcomes of extended-pulsed fidaxomicin compared with vancomycin, with a primary efficacy endpoint of sustained clinical cure of *C difficile* infection 30 days after the end of treatment, in a microbiota-sparing strategy.

Methods

Study design and patients

We did a phase 3b/4, randomised, controlled, parallel, superiority, open-label trial at 86 hospitals in 21 European countries. Hospitalised patients were eligible for inclusion if they were aged 60 years and older with clinically confirmed *C difficile* infection, defined by either more than three unformed bowel movements or at least 200 mL unformed stool (for patients with rectal collection devices) in the 24 h before randomisation, in addition to presence of *C difficile* toxin A or B in stool within 48 h of randomisation by local laboratory *C difficile* infection toxin test. Key exclusion criteria included *C difficile* infection therapy for more than 1 day within the past 48 h and more than two previous *C difficile* infection episodes within 3 months of enrolment (see appendix for full list of exclusion criteria). Before the first patient was enrolled, there was a country-specific protocol amendment in

Germany at the request of the local ethics committee because of concerns over potential fidaxomicin overabsorption in patients with inflammatory bowel disease. Thus, patients with inflammatory bowel disease were also excluded from the study. Institutional review boards at each site approved the study protocol and amendments. Patients provided written informed consent.

Randomisation and masking

Patients were centrally randomly assigned (1:1), using an interactive web response system, to receive extended-pulsed fidaxomicin or vancomycin. Randomisation was stratified by baseline *C difficile* infection severity (severe or non-severe; severe defined as leucocyte count $>15\times10^9$ cells per L or rise in serum creatinine [>50% above a patient's normal level] or albumin <30 g/L), presence or absence of cancer (defined as diagnosis of cancer within 6 months of the study or ongoing therapy for cancer treatment), age (≥75 years or <75 years), or number of previous *C difficile* infection occurrences (zero, one, or two) in the 3 months before study entry, with a block size of four, which was agreed before entry. Patients were recruited by the study investigators at sites in Europe, Russia, and Turkey.

For **Qiime software** see http://qiime.org/

Patients could participate in pharmacokinetic and microbiome (16S rRNA sequencing) substudies to analyse the concentration of fidaxomicin in blood (plasma), and the microbiome profile in stool samples.

Procedures

Presence of *C difficile* infection was locally confirmed at the screening visit. Patients received commercially available oral fidaxomicin 200 mg film-coated tablets (Astellas Pharma Europe, Leiden, Netherlands) twice daily on days 1–5, then once daily on alternate days on days 7–25 (extended-pulsed fidaxomicin), or commercially available oral vancomycin 125 mg capsules (Xellia Pharmaceuticals, Copenhagen, Denmark), four times daily on days 1–10.

At the test of cure visit on day 12 for vancomycin and day 12 or day 27 for extended-pulsed fidaxomicin, *C difficile* infection assessments, severity score, and clinical response were assessed. Clinical response was based on European Society of Clinical Microbiology and Infectious Diseases criteria.[3] Sustained clinical cure, defined as clinical response at test of cure and no *C difficile* infection recurrence, was determined on days 40, 55, and 90 (end of follow-up). All other cases were deemed treatment failures for sustained clinical cure.

For patients with clinical response at test of cure, recurrence of *C difficile* infection was defined as return of diarrhoea after test of cure to an extent (according to the frequency of unformed bowel movements) that was greater than the frequency recorded on day 10 for the vancomycin arm or day 25 for the extended-pulsed fidaxomicin arm, confirmed by a local *C difficile* infection test positive for toxin A or B and requiring further therapy. Recurrence was assessed up to day 90.

Stool samples were collected for all patients at screening (day 0) and, in the case of treatment failure or *C difficile* infection recurrence, stool samples underwent microbiological testing at a central laboratory (LGC, Fordham, UK). Samples were tested for the presence of *C difficile* toxin A or B using a qualitative ELISA, and bacterial, parasitic, or viral enteric pathogens, including *C difficile*, according to established methods (PCR-based multiplex test; BioFire FilmArray Gastrointestinal Panel, Biomérieux, Marcy-l'Étoile, France).

Pharmacokinetic assessments were done on days 5, 12, and 27. Stool samples for overall microbial diversity (microbiota substudy) analysis were collected on days 0, 5, 12, 27, 40, and 55, and at unscheduled visits for treatment failure or *C difficile* infection recurrence, and were tested at LGC Genomics, Berlin, Germany. Total bacterial DNA was extracted and the 16S rRNA gene sequenced (Illumina MiSeq V3, Illumina, San Diego, CA, USA) to measure changes in bacterial diversity following treatment with extended-pulsed fidaxomicin or vancomycin (appendix). The Shannon index of α diversity was calculated using Qiime version 1.9.0.

Patients were followed up at least every 2 weeks to check for *C difficile* infection recurrence, adverse events, and concomitant medication. If the patient was discharged from hospital, this follow-up might have been done by telephone. Information was collected if patients died, were readmitted to hospital, or if they received treatment or diagnostic procedures as either an inpatient or outpatient (resource utilisation).

Outcomes

The primary efficacy endpoint was sustained clinical cure of *C difficile* infection at 30 days after end of treatment (day 40 for vancomycin and day 55 for extended-pulsed fidaxomicin). Secondary endpoints were sustained clinical cure of *C difficile* infection at days 40, 55, and 90 for both treatment groups; clinical response of *C difficile* infection at day 12 and at 2 days after end of treatment (day 12 or day 27 for both vancomycin and extended-pulsed fidaxomicin); rate of relapse at day 90 as determined by whole genome sequencing of *C difficile* isolates from patients who had documented recurrence after test of cure; time to resolution of diarrhoea from the start of treatment, sustained to test of cure (ie, time of the last unformed bowel movement the day before the first of two consecutive days of ≤3 unformed bowel movements, >50% reduction in number of stools, or >75% reduction in liquid stool volume); recurrence of *C difficile* infection at days 40, 55, and 90; time to *C difficile* infection recurrence after end of treatment (for patients with clinical response); disease-free survival after day 10 (for patients with clinical response); incidence of mortality and severity of adverse events at day 90; health-related quality of life up to day 55; and readmission and

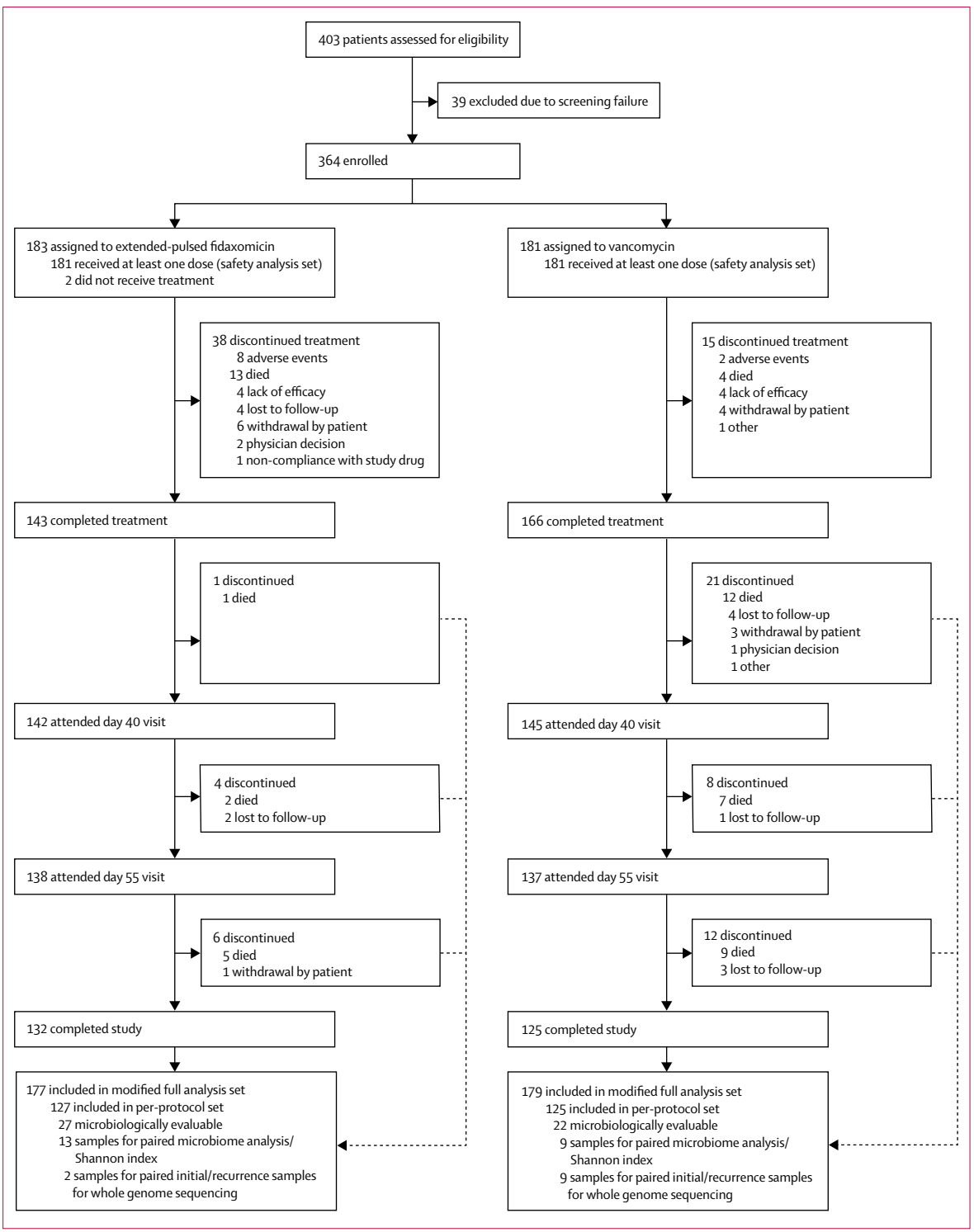

Figure 1: **Trial profile**

length of hospital stay at day 90. At the time of writing, data were not available on health-related quality of life, readmission, or length of stay, and these data will be reported separately. Exploratory endpoints included the number and volume of unformed bowel movements per day, and microbial diversity in stool samples. Safety was assessed from the first day of study treatment (day 1) to the end of study visit (day 90).

Adverse events were recorded at each study visit and assessed by a local investigator for severity and relationship to study drug. Adverse events of mild intensity were defined as those that did not disrupt normal daily activities.

Statistical analysis

To detect a difference between extended-pulsed fidaxomicin and vancomycin in relation to the primary endpoint, a maximum sample size of 346 patients (173 per arm) provided approximately 90% power at a two-sided overall significance level of 0·05. Assumptions were based on sustained clinical cure rates of 85% for extended-pulsed fidaxomicin and 70% for vancomycin (corresponding to an odds ratio [OR] of 2·43),[12,13] accounting for an interim analysis conducted after about 55% of patients with confirmed *C difficile* infection had completed the primary endpoint assessment. We planned to recruit an additional 18 patients to allow for incorrect inclusion of patients without positive *C difficile* culture confirmed at baseline.

Descriptive statistics are provided for continuous and categorical variables. All null hypotheses assumed no treatment difference and all alternative hypotheses were two-sided. Sustained clinical cure at 30 days after end of treatment was summarised by treatment group and the difference between the two treatment arms was compared across strata using the Cochran-Mantel-Haenszel test, adjusting for baseline stratification factors. Similar analyses were done for the secondary endpoints of sustained clinical cure at days 40, 55, and 90, clinical response (at day 12 and at 2 days after the end of treatment), and recurrence of *C difficile* infection (at days 40, 55, and 90). The significance level for comparison of the primary endpoint was 0·0425 for the final analysis. Additionally, multivariate analysis (logistic regression), which included treatment arm and baseline stratification factors as covariates, was done. If the primary endpoint differed significantly between treatment arms, then adjusted p values were obtained using the Hochberg procedure for endpoints of sustained clinical cure at days 40, 55, and 90, clinical response at day 12, and rate of relapse on day 90. For the endpoints time to *C difficile* infection recurrence after end of treatment, disease-free survival after day 10, and time to resolution of diarrhoea, the Kaplan-Meier method was used for the analyses and the stratified Wilcoxon-Gehan test used to compare survival (Kaplan-Meier) estimates. Time to resolution of diarrhoea was analysed using the Cox proportional hazards model, adjusting for treatment arm and baseline stratification factors. Differences in bacterial diversity were analysed using paired *t* tests.

Two study populations, the modified full analysis set and per-protocol set, were analysed for primary and secondary endpoints. The modified full analysis set comprised all randomised patients who met inclusion criteria and received at least one dose of study medication, and was the primary analysis set for efficacy. The per-protocol set comprised all patients in the modified full analysis set who had no major protocol deviations before assessment of the primary clinical endpoint and received at least 70% of the study treatment (appendix). The safety analysis set included all randomised patients who received at least one dose of study medication.

All analyses were done using SAS version 9.3. EXTEND is registered with ClinicalTrials.gov, number NCT02254967. An independent data monitoring committee continually reviewed drug safety.

	Extended-pulsed fidaxomicin (n=177)	Vancomycin (n=179)
Sex		
Female	107 (60%)	100 (56%)
Male	70 (40%)	79 (44%)
Race*		
White	149 (84%)	153 (85%)
Missing	28 (16%)	26 (15%)
Median age, years (IQR)	75 (69–83)	75 (67–82)
Number of unformed bowel movements per day		
Mean (SD)	6·8 (4·7)	6·4 (3·4)
Median (IQR)	5 (4–7)	5 (4–7)
Clostridium difficile infection severity†		
Severe	63 (36%)	67 (37%)
Non-severe	114 (64%)	112 (63%)
Number of previous *C difficile* infection occurrences in the past 3 months†		
0	141 (80%)	140 (78%)
1	26 (15%)	29 (16%)
2	10 (6%)	10 (6%)
Cancer status†		
Presence	38 (21%)	37 (21%)
Absence	139 (79%)	142 (79%)
Use of antibiotics for condition other than *C difficile* infection‡		
Yes	128 (72%)	129 (72%)
No	49 (28%)	50 (28%)
Residential setting before study enrolment		
Own residence	102 (58%)	103 (58%)
Family residence	66 (37%)	59 (33%)
Nursing home§	4 (2%)	6 (3%)
Long-term care facility§	1 (1%)	4 (2%)
Other	2 (1%)	7 (4%)
Missing	2 (1%)	0

Data are n (%) unless otherwise specified. *Not all study sites were permitted to report the race of patients, and in these cases this information was reported as missing. †Provided by interactive web response system at randomisation; type of cancer recorded only for medical history and not for analysis. ‡In the 90 days before the study. §A nursing home provides supportive care, whereas a long-term care facility provides rehabilitative care with a greater number of clinical personnel and facilities.

Table 1: **Baseline patient characteristics (modified full analysis set)**

Role of the funding source

The study sponsor was involved in all stages of the study, including manuscript development. The corresponding author had full access to all the data in the study and had

final responsibility for the decision to submit for publication.

Results

Between Nov 6, 2014, and May 5, 2016, 403 patients were screened for inclusion in the study. 39 patients were excluded due to screening failure and thus 364 patients were randomly assigned to receive extended-pulsed fidaxomicin or vancomycin (figure 1). 362 patients received at least one dose of study medication (181 received extended-pulsed fidaxomicin and 181 received vancomycin) and were included in the safety analysis (figure 1). Two patients randomised to extended-pulsed fidaxomicin did not have clinically confirmed *C difficile* and did not receive treatment.

Two patients in the vancomycin group and four in the extended-pulsed fidaxomicin group did not have confirmed *C difficile* infection, so were excluded from the modified full analysis set. Both treatment groups were similar regarding baseline characteristics, including age, *C difficile* infection severity, number of previous *C difficile* infection occurrences, and number of unformed bowel movements in the 24 h before randomisation (table 1).

For the primary efficacy endpoint, 124 (70%) of 177 patients in the extended-pulsed fidaxomicin group had sustained clinical cure at 30 days after end of treatment compared with 106 (59%) of 179 patients who received vancomycin (OR 1·62 [95% CI 1·04–2·54]; p=0·030, Cochran-Mantel-Haenszel test [primary analysis] and p=0·035, multivariate analysis; figure 2, table 2).

Results for the primary endpoint in the per-protocol set were similar to those in the modified full analysis set, with sustained clinical cure at 30 days after end of treatment higher in patients who received extended-pulsed fidaxomicin compared with those who received vancomycin (p=0·001; table 3). In the modified full analysis set only, multivariate analysis for sustained clinical cure at 30 days after end of treatment, adjusted for baseline stratification factors, showed that patients with severe *C difficile* infection were less likely to achieve sustained clinical cure than were patients with non-severe *C difficile* infection (table 2). Extended-pulsed fidaxomicin was associated with an increased rate of sustained clinical cure compared with vancomycin at 30 days after end of treatment in patients with PCR ribotype 027 infections (table 2). More patients in the extended-pulsed fidaxomicin arm than in the vancomycin arm achieved the secondary efficacy endpoint of sustained clinical cure at days 40, 55, and 90 in the modified full analysis set (table 2, figure 2) and per-protocol set (table 3).

At day 12 and day 27 (2 days after end of treatment), the clinical response to treatment did not differ between the extended-pulsed fidaxomicin and vancomycin study arms for the modified full analysis set (table 2, figure 2) and the per-protocol set (table 3).

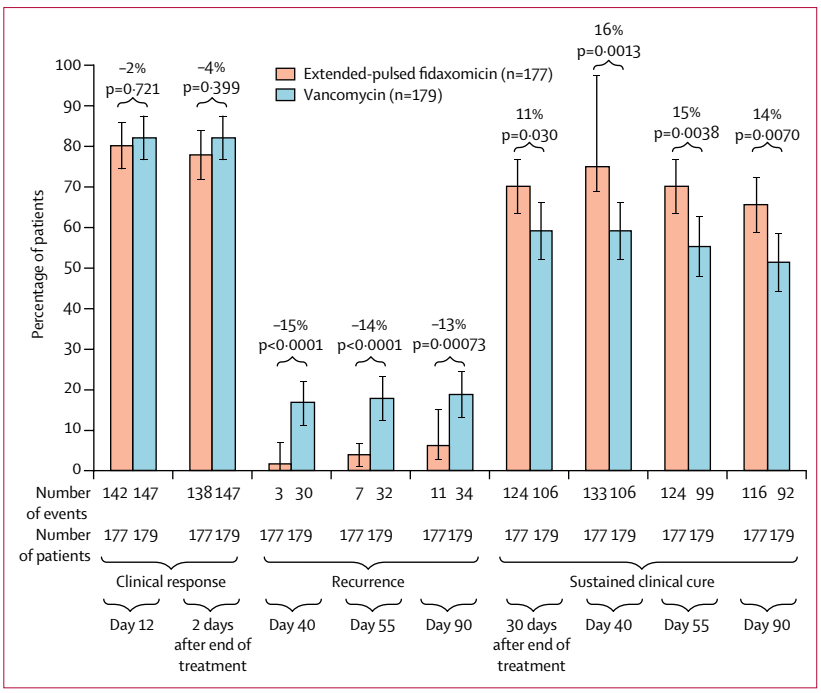

Figure 2: **Selected clinical outcomes**
Bars show 95% CI. Percentage increase or decrease for extended-pulsed fidaxomicin compared with vancomycin is shown above each pair of bars.

For patients who had clinical response to treatment at test of cure visit (day 12 for vancomycin and day 27 for extended-pulsed fidaxomicin), fewer patients in the extended-pulsed fidaxomicin than in the vancomycin arm had recurrence of *C difficile* infection at all three timepoints (day 40, day 55, and day 90; tables 2, 3; figure 2). At 30 days after end of treatment (day 55 for extended-pulsed fidaxomicin and day 40 for vancomycin), recurrence had occurred in seven (4%) patients receiving extended-pulsed fidaxomicin and 30 (17%) patients receiving vancomycin. Time to *C difficile* infection recurrence was longer after the end of treatment with extended-pulsed fidaxomicin than with vancomycin (p<0·0001; appendix).

The median time from start of treatment to resolution of diarrhoea appeared to favour vancomycin (censored at day 10, end of treatment) rather than extended-pulsed fidaxomicin (censored at day 25, end of treatment), although groups did not differ in the modified full analysis set (table 2) or the per-protocol set (table 3).

Most patients (127 of 137 extended-pulsed fidaxomicin patients and 114 of 147 vancomycin patients, of those who responded at test of cure) did not show symptoms of diarrhoea after day 10 and remained in the analysis until they discontinued or completed the study, after which they were censored. The time taken after day 10 for the first 5% of patients in the extended-pulsed fidaxomicin arm to have *C difficile* infection recurrence was 47 days (95% CI 23·0–not reached), compared with

9 days (95% CI 4·0–10·0) in the vancomycin arm. This overall difference in disease-free survival was significant (p=0·003; appendix). A hazard ratio of 0·26 (95% CI 0·12–0·50) was determined from a Cox proportional hazards model, adjusted for baseline stratification factors. This result suggests that the hazard of *C difficile* infection recurrence at any given time after day 10 for a vancomycin-treated patient was approximately 3·8-times that of an extended-pulsed fidaxomicin-treated patient.

The mean of the Shannon index of bacterial α diversity in stool samples was 3·39 (SD 0·93) at day 0

	Extended-pulsed fidaxomicin (n=177)	Vancomycin (n=179)	OR (95% CI)	p value
Clinical response at day 12*				
n (%)	142 (80%)	147 (82%)	0·91 (0·54–1·54)	0·721
OR by baseline stratification				
Clostridium difficile infection severe *vs* non-severe	..	..	0·42 (0·24–0·72)	0·0018
Presence *vs* absence of cancer	..	..	0·72 (0·39–1·35)	0·311
Age group ≥75 years *vs* <75 years	..	..	1·13 (0·65–1·96)	0·660
Previous *C difficile* infection occurrences (2 *vs* 0)	..	..	1·09 (0·30–3·96)	0·898
Previous *C difficile* infection occurrences (1 *vs* 0)	..	..	0·88 (0·42–1·84)	0·733
Clinical response 2 days after end of treatment (day 27 for extended-pulsed fidaxomicin or day 12 for vancomycin)*				
n (%)	138 (78%)	147 (82%)	0·81 (0·48–1·35)	0·399
OR by baseline stratification				
C difficile infection severe *vs* non-severe	..	..	0·54 (0·31–0·92)	0·025
Presence *vs* absence of cancer	..	..	0·49 (0·27–0·88)	0·016
Age group ≥75 years *vs* <75 years	..	..	0·94 (0·55–1·62)	0·825
Previous *C difficile* infection occurrences (2 *vs* 0)	..	..	1·27 (0·35–4·65)	0·715
Previous *C difficile* infection occurrences (1 *vs* 0)	..	..	0·83 (0·41–1·72)	0·624
Time to resolution of diarrhoea				
Median time (h) to resolution (95% CI)	34·0 (25·0–49·0)	22·0 (10·0–30·0)	..	0·068
Patients with unformed bowel movements on day 5 of treatment†				
0 per day	64 (40%) [n=160]	69 (41%) [n=170]	..	..
1–2 per day	51 (32%) [n=160]	67 (39%) [n=170]	..	..
≥3 per day	45 (28%) [n=160]	34 (20%) [n=170]	..	..
Patients with unformed bowel movements on day 12 of treatment‡				
0 per day	110 (74%) [n=148]	57 (74%) [n=77]	..	..
1–2 per day	29 (20%) [n=148]	16 (21%) [n=77]	..	..
≥3 per day	9 (6%) [n=148]	4 (5%) [n=77]	..	..
Patients with unformed bowel movements on day 25 of treatment§				
0 per day	115 (85%) [n=135]	..	..	..
1–2 per day	15 (11%) [n=135]	..	..	..
≥3 per day	5 (4%) [n=135]	..	..	..
Recurrence of *C difficile* infection				
At day 40	3 (2%)	30 (17%)	0·09 (0·03–0·29)	<0·0001
At day 55	7 (4%)	32 (18%)	0·20 (0·08–0·46)	<0·0001
At day 90	11 (6%)	34 (19%)	0·29 (0·14–0·60)	0·00073
Sustained clinical cure 30 days after end of treatment				
n (%)	124 (70%)	106 (59%)	1·62 (1·04–2·54)	0·030
OR by baseline stratification				
C difficile infection severe *vs* non-severe	..	..	0·57 (0·36–0·91)	0·019
Presence *vs* absence of cancer	..	..	0·59 (0·35–1·01)	0·053
Age group ≥75 years *vs* <75 years	..	..	0·83 (0·53–1·30)	0·414
Previous *C difficile* infection occurrences (2 *vs* 0)	..	..	0·69 (0·26–1·80)	0·444
Previous *C difficile* infection occurrences (1 *vs* 0)	..	..	0·61 (0·33–1·11)	0·105
Sustained clinical cure 30 days after end of treatment				
Presence of *C difficile* PCR ribotype 027¶	20 (80%) [n=25]	9 (41%) [n=22]	..	0·0059
Absence of *C difficile* PCR ribotype 027‖	104 (68%) [n=152]	97 (62%) [n=157]	..	0·221

(Table 2 continues on next page)

	Extended-pulsed fidaxomicin (n=177)	Vancomycin (n=179)	OR (95% CI)	p value
(Continued from previous page)				
Sustained clinical cure				
At day 40	133 (75%)	106 (59%)	2·10 (1·32–3·34)	0·0013
At day 55	124 (70%)	99 (55%)	1·91 (1·23–2·98)	0·0038
At day 90	116 (66%)	92 (51%)	1·80 (1·17–2·77)	0·0070
Clinical outcome by presence of enteric pathogen**				
Sustained clinical cure 30 days after end of treatment				
C difficile	103 (88%) [n=117]	86 (90%) [n=96]	..	..
Other pathogen	39 (33%) [n=117]	37 (39%) [n=96]	..	..
None detected	9 (8%) [n=117]	3 (3%) [n=96]	..	..
Recurrence				
C difficile	8 (4%) [n=181]	20 (11%) [n=181]	..	..
Other pathogen	1 (1%) [n=181]	4 (2%) [n=181]	..	..
None detected	1 (1%) [n=181]	5 (3%) [n=181]	..	..
Treatment failure				
C difficile	0	0	..	..
Other pathogen	0	1 (1%) [n=181]	..	..
None detected	2 (1%) [n=181]	2 (1%) [n=181]	..	..

Data are n (%) unless otherwise indicated. Number of patients analysed is presented in square brackets if data are missing. OR=odds ratio. *Difference between the rates (extended-pulsed fidaxomicin and vancomycin) and the associated 95% CI around the difference, day 12 −1·9% (−10·0 to 6·2), p=0·721 and 2 days after end of treatment −4·2% (−12·5 to 4·1), p=0·399. †Patients were censored at day 10 for vancomycin (240 h after start of treatment) and at day 25 for extended-pulsed fidaxomicin (600 h after start of treatment). ‡147 patients were not included in the analysis as they had no unformed bowel movement records provided up to day 13. §For the vancomycin arm, unformed bowel movement records were collected only up to day 12 (plus or minus 2 days). ¶Treatment difference 39·1 (95% CI 13·2–64·9). ||Treatment difference 6·6 (95% CI −4·0 to 17·2). **Pathogens detected by multiplex PCR testing of faecal samples at screening in the safety analysis set, at treatment failure, *Clostridium difficile* recurrence, or unscheduled event. Other pathogens included non-*C difficile* bacterial, parasitic, and viral enteric pathogens, identified according to established methods (appendix).

Table 2: **Clinical outcomes for the modified full analysis set**

and 4·47 (0·73) at day 55 for 13 extended-pulsed fidaxomicin-treated patients, and 3·49 (1·23) at day 0 and 3·20 (1·24) at day 55 for nine vancomycin-treated patients. The distribution of shift in Shannon index indicated that bacterial α diversity increased to a higher extent in extended-pulsed fidaxomicin-treated patients than in vancomycin-treated patients (median shift 0·83, IQR 0·51 to 1·68 *vs* −0·37, −0·80 to 0·79; figure 3) over the course of the study treatment and follow-up period.

Presence of *C difficile* and microbial pathogens other than *C difficile* was analysed by a central laboratory in 332 samples taken at screening using a PCR-based multiplex test. Of these samples, 88% (292 of 332) were positive for *C difficile* and 23% (76 of 332) were positive for a gastrointestinal pathogen other than *C difficile*, of which enteropathogenic *Escherichia coli* was the most commonly identified (29 [9%] of 332; appendix).

Plasma pharmacokinetic analysis revealed low concentrations of fidaxomicin from days 5 to 25 or 26 (sampling depended on timing of extended-pulsed fidaxomicin dosing), in the range 3·75–175 ng/mL at 1–5 h after dosing. Median plasma fidaxomicin concentrations decreased in line with the change in dosing scheme. There was no accumulation of fidaxomicin in plasma over the extended dosing period.

Overall, the safety profile of extended-pulsed fidaxomicin seemed similar to that of the vancomycin regimen (table 4). 87 (48%) of 181 adverse events in the extended-pulsed fidaxomicin group and 91 (50%) of 176 in the vancomycin group were classified as mild. Serious adverse events occurred in 68 (38%) extended-pulsed fidaxomicin-treated patients and 78 (43%) vancomycin-treated patients. Three (2%) patients receiving extended-pulsed fidaxomicin and six (3%) patients receiving vancomycin had drug-related serious adverse events. The drug-related serious adverse events in the extended-pulsed fidaxomicin arm were one event (1%) each of pruritus, bile duct stone, and drug hypersensitivity; the latter two adverse events led to permanent discontinuation of study drug. The drug-related serious adverse events in the vancomycin arm were one event each of cardiac failure, ileus (leading to permanent discontinuation of study drug), treatment failure, *Clostridium* spp infection, *Klebsiella* spp infection, sepsis, somnolence, and eczema.

65 (18%) deaths occurred during the study, with 29 (16%) in the extended-pulsed fidaxomicin arm and 36 (20%) in the vancomycin arm (appendix). Only one death was related to study drug (as assessed by the investigator)—a 73-year-old woman in the vancomycin arm who died of sepsis and heart failure on day 12 (appendix).

	Extended-pulsed fidaxomicin (n=124)	Vancomycin (n=125)	OR (95% CI)	p value
Clinical response at day 12*				
n (%)	111 (90%)	109 (87%)	1·22 (0·55–2·70)	0·621
OR by baseline stratification				
Clostridium difficile infection severe *vs* non-severe	..	..	0·56 (0·25–1·26)	0·160
Presence *vs* absence of cancer	..	..	0·99 (0·35–2·78)	0·985
Age group ≥75 years *vs* <75 years	..	..	0·91 (0·40–2·05)	0·818
Previous *C difficile* infection occurrences (2 *vs* 0)	..	..	0·96 (0·20–4·60)	0·955
Previous *C difficile* infection occurrences (1 *vs* 0)	..	..	1·20 (0·39–3·71)	0·754
Clinical response 2 days after end of treatment (day 27 for extended-pulsed fidaxomicin or day 12 for vancomycin)*				
n (%)	116 (94%)	109 (87%)	1·97 (0·81–4·79)	0·131
OR by baseline stratification				
C difficile infection severe *vs* non-severe	..	..	1·33 (0·49–3·60)	0·575
Presence *vs* absence of cancer	..	..	0·74 (0·26–2·14)	0·583
Age group ≥75 years *vs* <75 years	..	..	0·78 (0·32–1·89)	0·579
Previous *C difficile* infection occurrences (2 *vs* 0)	..	..	0·80 (0·16–3·90)	0·778
Previous *C difficile* infection occurrences (1 *vs* 0)	..	..	0·72 (0·24–2·10)	0·544
Time to resolution of diarrhoea				
Median time (h) to resolution (95% CI)	28·5 (22·0–42·0)	13·0 (8·0–26·0)	..	0·113
Patients with unformed bowel movements on day 5 of treatment†				
0 per day	49 (40%)	50 (40%)	..	..
1–2 per day	40 (32%)	54 (43%)	..	..
≥3 per day	35 (28%)	21 (17%)	..	..
Patients with unformed bowel movements on day 12 of treatment‡				
0 per day	91 (73%)	45 (71%) [n=63]	..	..
1–2 per day	25 (20%)	15 (24%) [n=63]	..	..
≥3 per day	8 (6%)	3 (5%) [n=63]	..	..
Patients with unformed bowel movements on day 25 of treatment§				
0 per day	101 (86%) [n=117]	..	..	..
1–2 per day	12 (10%) [n=117]	..	..	..
≥3 per day	4 (3%) [n=117]	..	..	..
Recurrence of *C difficile* infection				
At day 40	3 (2%)	22 (18%)	0·12 (0·04–0·41)	<0·0001
At day 55	7 (6%)	23 (18%)	0·31 (0·13–0·73)	0·0032
At day 90	11 (9%)	23 (18%)	0·49 (0·23–1·04)	0·048
Sustained clinical cure 30 days after end of treatment¶				
n (%), 95% CI	106 (85·5%), 79·3–91·7	83 (66·4%), 58·1–74·7	2·99 (1·52–5·90)	0·0011
OR by baseline stratification				
C difficile infection severe *vs* non-severe	..	..	1·49 (0·73–3·04)	0·273
Presence *vs* absence of cancer	..	..	0·62 (0·29–1·35)	0·227
Age group ≥75 years *vs* <75 years	..	..	0·54 (0·28–1·02)	0·059
Previous *C difficile* infection occurrences (2 *vs* 0)	..	..	0·53 (0·18–1·63)	0·270
Previous *C difficile* infection occurrences (1 *vs* 0)	..	..	0·43 (0·20–0·92)	0·030
Sustained clinical cure				
At day 40	113 (91%)	83 (66%)	5·83 (2·61–13·05)	<0·0001
At day 55	106 (85%)	78 (62%)	3·61 (1·84–7·07)	<0·0001
At day 90	100 (81%)	75 (60%)	2·71 (1·48–4·96)	0·0011

Data are n (%) unless otherwise indicated. Number of patients analysed is presented in square brackets if data are missing. OR=odds ratio. *Difference between the rates (extended-pulsed fidaxomicin and vancomycin) and the associated 95% CI around the difference, day 12 2·3% (−5·6 to 10·3), p=0·621 and at 2 days after end of treatment 6·3% (−0·9 to 13·6), p=0·131. †Patients were censored at day 10 (240 h after start of treatment) for vancomycin and day 25 (600 h after start of treatment) for extended-pulsed fidaxomicin. ‡99 patients were not included in the analysis as they had no unformed bowel movement records provided up to day 13. §For the vancomycin arm, unformed bowel movement records were collected only up to day 12 (plus or minus 2 days). ¶Treatment difference 19·1 (8·7–29·4; p=0·0011).

***Table 3*: Clinical outcomes for the per-protocol set**

Discussion

In this multicentre, randomised *C difficile* infection study testing the concept of pulsed dosing as a microbiota-sparing strategy, extended-pulsed fidaxomicin was superior to standard-dose vancomycin for the primary endpoint of sustained clinical cure of *C difficile* infection in patients aged 60 years and older. Crucial to the achievement of sustained clinical cure, the recurrence rate observed in the present study was lower in the extended-pulsed fidaxomicin arm than in the vancomycin arm at every visit up to day 90. The recurrence rate at day 90 in the extended-pulsed fidaxomicin arm (6%) was lower than was reported in previous randomised, controlled studies of standard regimens of fidaxomicin, vancomycin, and metronidazole.[3,12,13] A recurrence rate of 8–26%, depending on previous recurrence, was observed in a real-world study of fidaxomicin.[16] Follow-up to day 90, as in our study, is unusual and gives added insight and, to our knowledge, such a long follow-up has only been reported in the registration study of the monoclonal antibody bezlotoxumab.[17]

Although the sustained clinical cure of *C difficile* infection achieved at 30 days after the end of extended-pulsed fidaxomicin treatment in our study (70%) was similar to that achieved in phase 3 studies with a standard twice-daily, 10-day course of fidaxomicin (214 [75%] of 287 patients;[13] 221 [88%] of 252 patients[12]), the results of these previous studies are not directly comparable to ours because of differences in study design and outcome criteria. Patients in EXTEND were older than were those in previous studies (mean 75·1 years [SD 8·7] compared with 61·6 years [16·9][13] and 63·4 years [18·1][12]) to stress test the regimen, and the recurrence rate was substantially lower at 90 days with extended-pulsed fidaxomicin in EXTEND (6%) than it was at 40 days with standard fidaxomicin in previous phase 3 studies (39 [15%] of 253 patients;[13] 28 [13%] of 221 patients[12]).

Patients older than 65 years have a greater relative risk of *C difficile* infection recurrence than do younger patients, and patients aged at least 75 years have a higher odds ratio for mortality before 30 days.[18] The reduction in recurrence rates observed with extended-pulsed fidaxomicin compared with previous studies suggests potential health-care benefits beyond the studied clinical endpoints. In the extended-pulsed fidaxomicin regimen, the same number of fidaxomicin tablets is administered as in the standard licensed regimen, but enhanced outcomes are seen compared with vancomycin, potentially resulting in a cost-effectiveness benefit. Additionally, as *C difficile* infection recurrence has high cost implications, avoidance of recurrence is considered economically important, particularly in high-risk patients.[19] For every seven patients treated with fidaxomicin, an estimated one hospital readmission for *C difficile* infection is prevented compared with patients treated with vancomycin.[20] In our study of an older patient population, the number needed to treat with extended-pulsed fidaxomicin is estimated at 6·6, derived from the absolute difference in recurrence rate with vancomycin at a similar timepoint of 40 days. Recurrence rates observed in the vancomycin arm were lower than those previously reported in the vancomycin arm of fidaxomicin phase 3 registration trials.[12,13] Epidemiological changes, differences in antimicrobial stewardship and infection control, and differences in the characteristics or treatment of the patient population might have contributed to this reduction in recurrence with vancomycin. However, reported recurrence rates with

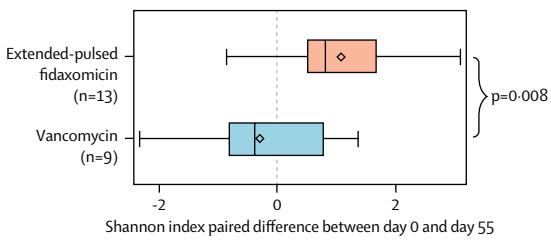

Figure 3: **Distribution of shift in Shannon index of faecal microbiota α diversity from day 0 to day 55**
Paired comparison of mean (SD) α diversity from day 0 to day 55 for extended-pulsed fidaxomicin was 1·08 (0·96), p=0·0015, and for vancomycin was -0·29 (1·25), p=0·5056. Box shows 25–75th percentile, vertical line shows median, and diamond shows mean. Whiskers show range.

	Extended-pulsed fidaxomicin (n=181)	Vancomycin (n=181)
Any treatment-emergent adverse event	121 (67%)	128 (71%)
Any severe treatment-emergent adverse event*	44 (24%)	56 (31%)
Any treatment-emergent adverse event related to study drug†	14 (8%)	9 (5%)
Any serious treatment-emergent adverse event‡	68 (38%)	78 (43%)
Any treatment-emergent adverse event leading to discontinuation of study drug§	14 (8%)	5 (3%)
Any treatment-emergent adverse event causing death	3 (2%)	3 (2%)
Adverse event by preferred term¶		
Anaemia	5 (3%)	10 (6%)
Cardiac failure	4 (2%)	10 (6%)
Constipation	10 (6%)	5 (3%)
Diarrhoea	10 (6%)	12 (7%)
Pyrexia	7 (4%)	12 (7%)
Clostridium spp infection‖	7 (4%)	24 (13%)
Pneumonia	5 (3%)	10 (6%)
Sepsis	1 (1%)	9 (5%)
Urinary tract infection	6 (3%)	12 (7%)

Data are presented as n (%). *Defined as adverse events causing inability to perform daily activities. †Possibly or probably related to study drug, as assessed by the investigator, or records where relationship was missing. ‡Defined as adverse events resulting in death, or considered to be life-threatening, requiring hospitalisation, or resulting in persistent or substantial disability or incapacity, congenital anomaly, or other medically important events. §A woman aged 79 years had drug hypersensitivity (rash and bronchospasm) of moderate intensity on treatment day 3. The event was considered serious and probably related to treatment. Dechallenge with enhanced-pulsed fidaxomicin was positive. Enhanced-pulsed fidaxomicin was permanently withdrawn. The event resolved on day 7 after treatment for hypersensitivity. This side-effect is noted on the fidaxomicin label.[15] ¶Reported in at least 5% of patients in any treatment group. ‖All treatment-emergent adverse advents recorded as *Clostridium* spp infection were *Clostridium difficile* infection.

Table 4: **Treatment-emergent adverse events**

vancomycin in this study align with reported recurrence rates in a retrospective cohort study.[21]

In phase 3 studies, no significant difference in efficacy was observed between fidaxomicin and vancomycin in patients with PCR ribotype 027 infections.[13] In our study, extended-pulsed fidaxomicin was associated with an increased rate of sustained clinical cure compared with vancomycin at 30 days after end of treatment in this patient subgroup. However, as with previous studies, EXTEND was not sufficiently powered to permit strong conclusions on differences in efficacy in patients with PCR ribotype 027 infections.

Vancomycin therapy is detrimental to the gut microbiota, with depletion of many bacterial types (operational taxonomic units), particularly from the Bacteroidetes phylum, and the proportion of several organisms associated with human infection, such as *Klebsiella* spp, *Escherichia* spp, vancomycin-resistant enterococci, and *Candida* spp, is increased after treatment.[11,22] Analysis of the Shannon index of α diversity indicated that extended-pulsed fidaxomicin enhanced microbiota recovery over our study period to a significantly higher degree than did vancomycin, providing support for extended-pulsed fidaxomicin as a microbiota-sparing treatment strategy. This increased microbial diversity in patients treated with extended-pulsed fidaxomicin will be of interest for future studies, and suggests a possible mechanistic basis for the reduced recurrence rates observed in this study.

More deaths occurred in the vancomycin arm of our study, but of greater interest is the higher number of deaths among vancomycin recipients after day 27. Recurrence has been found to be associated with increased mortality by day 90 after hospital discharge.[23]

A limitation of our study is the absence of standard fidaxomicin or extended-pulsed vancomycin arms. Although additional treatment arms offer improved certainty and depth of information, they also represent a major cost driver in clinical trials, which can limit their feasibility. Furthermore, vancomycin is considered the standard of care for *C difficile* infection and was therefore the most appropriate comparator arm.[3] In the present setting, data from previous studies provide sufficient insight to justify omission of additional treatment arms. In-vitro data from a gut model of *C difficile* infection primed with faeces from an older population (aged >60 years) do not suggest that incorporating standard and extended-pulsed regimens of fidaxomicin would differ in terms of efficacy in resolving *C difficile* infection,[14] and our observed similarity in clinical response rates at day 12 between extended-pulsed fidaxomicin and vancomycin supports this hypothesis. This observation, combined with data from randomised clinical studies showing a recurrence rate of 15·4% or lower for the standard fidaxomicin regimen,[12,13] suggests outcomes that are at least as good for extended-pulsed fidaxomicin compared with standard fidaxomicin; however, a future indirect treatment comparison of these regimens could be of interest to further understand their relative effectiveness. Retrospective observational data suggest potential efficacy of extended-pulsed vancomycin for recurrent *C difficile* infection.[24] However, laboratory studies have shown the disruptive effect of vancomycin on gut microbiota,[25] and such an extended regimen could further exacerbate post-treatment gut microbiota dysbiosis.

This study's definition of *C difficile* infection recurrence—based on worsening symptoms—reflected clinical practice, but could be perceived as yielding a low threshold for examining recurrence. Nevertheless, diagnosis required the investigator to treat for recurrence based on their clinical judgment. The absence of blinding and insufficient racial diversity in the study population might also be considered limitations of this study. Furthermore, the study does not provide information on the use of extended-pulsed fidaxomicin in patients younger than 60 years, or in those with at least three *C difficile* infection recurrences.

Our study has many strengths, including, to our knowledge, the first demonstration in a randomised clinical trial setting of a *C difficile* infection recurrence rate less than 7% by optimising the delivery of an already available antibiotic. This hypothesis-driven study uses our understanding of *C difficile* infection pathogenesis and the method of action of fidaxomicin to enhance the dosing regimen and improve outcomes in a high-risk patient population. 90-day follow-up provided an extensive period over which reinfection or recurrence could be studied and gave important new data on *C difficile* infection recurrence. Incorporation of a microbiota substudy analysis also provided evidence to explain and validate observed clinical outcomes.

EXTEND is an uncommon positive superiority antibiotic trial, showing an improvement in sustained clinical cure of *C difficile* infection with extended-pulsed fidaxomicin and a significant reduction in recurrence rates compared with vancomycin treatment, even up to day 90, with simultaneous enhanced microbiota recovery. Since the extended-pulsed regimen of fidaxomicin administers the same number of tablets as the standard regimen, the observed benefits are derived with no increase in treatment costs and with a similar positive safety profile to that of standard-regimen vancomycin and fidaxomicin. Furthermore, the *C difficile* recurrence rate of 4% at 30 days after end of treatment is, to date, the lowest observed in a randomised clinical trial.

Contributors

AK and CL developed the extended-pulsed fidaxomicin regimen and, together with NA, conceived the study. BG, FM, V-JA, NA, AK, GK, JMA, KB, AG, SDG, CL, JAP-F, OAC, and MJGTV contributed to study design and execution. All authors contributed to the collection, interpretation and analysis of data, and preparation of the manuscript. The manuscript was reviewed, edited, and approved by all authors, who vouch for the accuracy and completeness of the data obtained and for adherence with the trial's protocol.

Declaration of interests
BG has received honoraria for speaking or participating in advisory boards, and research grants from Pfizer and Astellas. V-JA has received lecture fees from Astellas, MSD, Roche, and Pfizer, and funding to attend congresses from Astellas and Pfizer. SDG has received grants and personal fees from Astellas. JMA has received honoraria for speaking or participating in advisory boards and research grants from Gilead Sciences, Pfizer, Roche, Merck, and Novartis. AK, NA, AG, and JAP-F are full-time employees of Astellas Pharma. CL was a full-time employee of Astellas Pharma, Inc, during the study conduct and is now an employee of Basilea Pharmaceuticals. AK and CL have a patent WO2015169451 A1, and AK and JAP-F have a patent EP17167541.6, both pending to Astellas Pharma Europe Ltd. GK is a consultant statistician working on behalf of Astellas Pharma, Inc. OAC has received grants from Actelion, Aranis, Astellas, AstraZeneca, Basilea, Bayer, Cidara, Duke University, F2G, Gilead, GSK, Leeds University, MedPace, Melinta Therapeutics, Merck/MSD, Miltenyi, Pfizer, Rempex, Roche, Sanofi Pasteur, Scynexis, Seres Therapeutics, and The Medicines Company; and personal fees for consulting or advisory boards from Actelion, Amplyx, Anacor, Astellas, Basilea, Cidara, Da Volterra, F2G, Gilead, Janssen Pharmaceuticals, Matinas, Menarini Richerche, Merck/MSD, Paratek Pharmaceuticals, Scynexis, Seres Therapeutics, Summit, Vical, and Vifor. MJGTV has been a consultant to Berlin Chemie, MSD/Merck, and Astellas Pharma; served at the speakers' bureaus of Pfizer, Merck/MSD, Gilead Sciences, Organobalance, and Astellas Pharma; and received research funding from 3M, Astellas Pharma, Merck/MSD, Organobalance, Da Volterra, Seres Therapeutics, and Gilead Sciences. KB has received personal fees for consulting from Astellas Pharma. FM declares no competing interests.

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References
1 Bouza E. Consequences of *Clostridium difficile* infection: understanding the healthcare burden. *Clin Microbiol Infect* 2012; **18** (suppl 6)**:** 5–12.
2 Bauer MP, Notermans DW, van Benthem BH, et al. *Clostridium difficile* infection in Europe: a hospital-based survey. *Lancet* 2011; **377:** 63–73.
3 Debast S, Bauer M, Kuijper E. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect* 2014; **20:** 1–26.
4 Karas JA, Enoch DA, Aliyu SH. A review of mortality due to *Clostridium difficile* infection. *J Infect* 2010; **61:** 1–8.
5 Aguado JM, Anttila VJ, Galperine T, et al. Highlighting clinical needs in *Clostridium difficile* infection: the views of European healthcare professionals at the front line. *J Hosp Infect* 2015; **90:** 117–25.
6 Heimann SM, Vehreschild JJ, Cornely OA, et al. Economic burden of *Clostridium difficile* associated diarrhoea: a cost-of-illness study from a German tertiary care hospital. *Infection* 2015; **43:** 707–14.
7 Mizusawa M, Doron S, Gorbach S. *Clostridium difficile* diarrhea in the elderly: current issues and management options. *Drugs Aging* 15; **32:** 639–47.
8 Britton RA, Young VB. Interaction between the intestinal microbiota and host in *Clostridium difficile* colonization resistance. *Trends Microbiol* 2012; **20:** 313–19.
9 Buffie CG, Bucci V, Stein RR, et al. Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. *Nature* 2015; **517:** 205–08.
10 Louie TJ, Cannon K, Byrne B, et al. Fidaxomicin preserves the intestinal microbiome during and after treatment of *Clostridium difficile* infection (CDI) and reduces both toxin reexpression and recurrence of CDI. *Clin Infect Dis* 2012; **55** (suppl 2)**:** S132–42.
11 Isaac S, Scher JU, Djukovic A, et al. Short- and long-term effects of oral vancomycin on the human intestinal microbiota. *J Antimicrob Chemother* 2017; **72:** 128–36.
12 Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis* 2012; **12:** 281–89.
13 Louie TJ, Miller MA, Mullane K, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 2011; **364:** 422–31.
14 Chilton CH, Crowther GS, Todhunter SL, et al. Efficacy of alternative fidaxomicin dosing regimens for treatment of simulated *Clostridium difficile* infection in an in vitro human gut model. *J Antimicrob Chemother* 2015; **70:** 2598–607.
15 Iarikov DE, Alexander J, Nambiar S. Hypersensitivity reactions associated with fidaxomicin use. *Clin Infect Dis* 2014; **58:** 537–39.
16 Pichenot M, Héquette-Ruz R, Le Guern R, et al. Fidaxomicin for treatment of *Clostridium difficile* infection in clinical practice: a prospective cohort study in a French University Hospital. *Infection* 2017; **45:** 425–31.
17 Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N Engl J Med* 2017; **376:** 305–17.
18 Chakra CNA, Pepin J, Sirard S, Valiquette L. Risk factors for recurrence, complications and mortality in *Clostridium difficile* infection: a systematic review. *PLoS One* 2014; **9:** e98400.
19 Nathwani D, Cornely OA, Van Engen AK, Odufowora-Sita O, Retsa P, Odeyemi IA. Cost-effectiveness analysis of fidaxomicin versus vancomycin in *Clostridium difficile* infection. *J Antimicrob Chemother* 2014; **69:** 2901–12.
20 Sclar DA, Robison LM, Oganov AM, Schmidt JM, Bowen KA, Castillo LV. Fidaxomicin for *Clostridium difficile*-associated diarrhoea: epidemiological method for estimation of warranted price. *Clin Drug Investig* 2012; **32:** e17–24.
21 Stevens VW, Nelson RE, Schwab-Daugherty EM, et al. Comparative effectiveness of vancomycin and metronidazole for the prevention of recurrence and death in patients with *Clostridium difficile* infection. *JAMA Intern Med* 2017; **177:** 546–53.
22 Nerandzic MM, Mullane K, Miller MA, Babakhani F, Donskey CJ. Reduced acquisition and overgrowth of vancomycin-resistant enterococci and *Candida* species in patients treated with fidaxomicin versus vancomycin for *Clostridium difficile* infection. *Clin Infect Dis* 2012; **55** (suppl 2)**:** S121–26.
23 Olsen MA, Yan Y, Reske KA, Zilberberg MD, Dubberke ER. Recurrent *Clostridium difficile* infection is associated with increased mortality. *Clin Microbiol Infect* 2015; **21:** 164–70.
24 Sirbu BD, Soriano MM, Manzo C, Lum J, Gerding DN, Johnson S. Vancomycin taper and pulsed regimen with careful follow up for patients with recurrent *Clostridium difficile* infection. *Clin Infect Dis* 2017; **65:** 1396–99.
25 Crowther GS, Chilton CH, Longshaw C, et al. Efficacy of vancomycin extended-dosing regimens for treatment of simulated *Clostridium difficile* infection within an in vitro human gut model. *J Antimicrob Chemother* 2016; **71:** 986–91.